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Nonpolioviruses and Paralytic Disease

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• **A number of nonpolioviruses have been implicated as the probable etiologic agents of paralytic illness clinically resembling poliomyelitis, including certain immunotypes of Coxsackie group A, Coxsackie group B, and ECHO viruses, and the viruses of mumps, herpes simplex and arthropod-borne encephalitides. A number of well documented cases provide evidence that some of these viruses may on occasion be the causative agents of severe, even fatal, myelitis, bulbomyelitis or encephalomyelitis, but they have been associated much more frequently with cases of "poliomyelitis" in which there has been slight to moderate paresis. In the aggregate, various "nonpolioviruses" have been encountered in approximately 10 per cent of the patients with clinical poliomyelitis studied, but it is uncertain how many of these cases may represent coincidental infections not causally related to the current illness.**

THE WORK OF ENDERS and associates[7] published in 1949 showing that polioviruses could be propagated *in vitro* in cultures of various non-neural tissues opened the way to the development simultaneously of practical methods for the laboratory diagnosis of poliomyelitis and of formalin-inactivated poliovirus vaccines (Salk type). These two developments led in turn to the increasing recognition of illnesses diagnosed clinically as paralytic poliomyelitis in which laboratory evidence of poliovirus infection could not be found and other viral infections were implicated.

This communication will review briefly some of the recorded observations implicating various "nonpolioviruses" in paralytic disease and summarize the results of virologic studies of cases of clinical paralytic poliomyelitis made in this laboratory since 1956. In this context, the term "paralysis" is used broadly, as is commonly done in the clinical diagnosis of poliomyelitis, to include any clearly demonstrable weakness of localized muscle groups, as opposed to generalized weakness that persists after the acute febrile phase of illness has subsided. It is apparent that this liberal definition includes instances of transient weakness which may be of no permanent consequence to the patient, and that further characterization of paralysis with respect to extent and duration is needed to evaluate the seriousness of disability which may ensue.

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Viral infections to be considered in paralytic illnesses

Common Exanthemas of childhood. Involvement of the central nervous system (CNS) associated with measles (rubeola), rubella and chickenpox may take diverse forms, but the clinical features are most commonly those of diffuse or multifocal

encephalitis or encephalomyelitis, including such signs as irritability, convulsions, drowsiness or coma, confusion, aphasia and ataxia.[22,24,31] Thus these infections are not commonly considered in the clinical category of paralytic disease. However, in rare cases of post-measles CNS disease, signs of spinal cord involvement have been predominant,[31] and the occurrence of cranial nerve palsies or respiratory center involvement may in some cases simulate bulbar poliomyelitis. The incidence of post-infectious encephalomyelitis following the common childhood exanthemas is given in a recent review[24] as approximately 1 in 700 cases of measles, 1 in 6,000 cases of rubella and 1 in 6,000 to 10,000 cases of chickenpox.

Herpes simplex. In primary infections, the herpes simplex virus may involve the central nervous system, giving rise to a varied clinical picture ranging from benign meningitis to severe encephalomyelitis. Among the variable manifestations are coma, convulsions, ocular palsies, paresis of muscle groups and sensory changes.[28] Ocular palsies or spinal cord involvement may clinically suggest poliomyelitis. CNS involvement may be the only clinical manifestation of herpes virus infection or may be accompanied by characteristic herpetic lesions of the skin or mucous membranes. CNS involvement is not known to be associated with recurrent episodes of herpetic disease.

Mumps. The mumps virus is now recognized as one of the most common etiologic agents of aseptic meningitis or mild meningoencephalitis, characterized by headache, pleocytosis, signs of meningeal irritation and varying degrees of drowsiness. Although often referred to as a complication, this clinical picture apparently results from direct invasion of the CNS, at least of the meninges, as one of the alternative sites of localization of the virus in the course of mumps virus infection. Thus this syndrome may accompany, follow, precede, or occur without parotitis or other manifestations of mumps virus infection and is commonly estimated to occur in 5 to 10 per cent of all cases of clinical mumps. In some instances the signs of meningitis or meningoencephalitis may be accompanied by muscle pain, tightness of the hamstrings and localized paresis—resembling poliomyelitis. A series of 11 cases of mumps virus infection initially diagnosed clinically as spinal paralytic poliomyelitis was recently described in a report[17] from this laboratory. All the patients were children from 1 to 11 years of age. Four of the patients were referred from the infectious disease service to secondary hospitals for convalescent care because of persistent muscle weakness and tightness. Also, in four instances slight residual weakness was still detectable on follow-up muscle examinations two to five months after onset.

More severe neurologic involvement similar to the demyelinating type of post-infectious encephalomyelitis has also been observed, though rarely, in mumps virus infection.[22,24]

The enteroviruses. The family of human enteroviruses now includes some 60 different agents, most of which have come to light only within the last ten years. There are unsettled questions regarding ultimate classification, but the enteroviruses are currently divided into four major groups: polioviruses (3 types), group A Coxsackie viruses (24 types), group B Coxsackie viruses (6 types) and ECHO viruses (29 types). While it is convenient to refer collectively to "Coxsackie viruses" or "ECHO (entero-cytopathogenic human orphan) viruses," each virus type is antigenically distinct. With the absence of commonly shared antigens, attempts to identify infection with these agents by means of antibody assays of paired serum specimens from patients require a separate serologic test for each type. Thus laboratory diagnosis of an enterovirus infection generally rests upon recovery and identification of the specific viral type augmented by antibody assays for the type of virus recovered.

CNS illnesses associated with "nonpolio" enteroviruses

Aseptic meningitis or meningoencephalitis has been associated with many types of Coxsackie and ECHO viruses through epidemiologic, clinical and laboratory observations, including recovery of a number of virus types from the blood or spinal fluid.[8,14,34] Reports of more severe neurologic disease have been relatively uncommon but several types of Coxsackie and ECHO viruses have been implicated in illnesses resembling paralytic poliomyelitis, ranging in severity from slight paresis to severe and fatal bulbospinal disease, and also in serious encephalomyelitic syndromes. Some of the published observations relative to the role of Coxsackie and ECHO viruses in neurologic diseases are outlined in Table 1.

The most extensive observations have concerned Coxsackie virus, type A7. Several strains of this virus were isolated in Russia in 1952 from two patients with apparent bulbospinal poliomyelitis, and this agent was considered for a time to be "type 4 poliovirus." Subsequent study showed it to be immunogenically similar to American strains of Coxsackie A7.[3] In the United States, one case of clinical poliomyelitis in a three-year-old boy with right lower facial weakness and paresis of the right lower extremity caused by Coxsackie A7 was described by Steigman.[29] Grist,[10] in Scotland, reported

TABLE 1.—*Association of Coxsackie and ECHO Viruses with Neurologic Disease*

Virus Type	Association with Neurologic Disease	References†
COXSACKIE GROUP A:		
A7	Recovered from feces of patients with spinal and bulbar paralysis; some fatal cases. Described in Russia as poliovirus, type 4. Produced neuronal lesions in monkeys.	3,* 10, 14,* 29*
A9	Recovered from feces of patients with predominantly mild spinal paralytic illnesses; occasionally severe paresis.	11, 12, 14,* 18
Other types	A2 recovered from CNS in infant deaths. A4 and A14 produced neuronal lesions in monkeys. Possible synergism between other Group A viruses and poliovirus?	3,* 4, 8*
COXSACKIE GROUP B:		
B2-B5	Recovered from feces of patients with mild to moderate spinal paralytic illnesses in which poliovirus was excluded.	3,* 12, 14,* 18, 21, 29*
B2, B3, B4	Recovered from brain and/or spinal cords of infants with encephalomyelitis and myocarditis. B2 produced neuronal lesions in monkeys.	2, 15*
B3	Recovered from spinal cord of patient with fatal spinal paralytic disease.	12
ECHO VIRUSES:		
E2	Recovered from spinal cord of patient with fatal bulbo-respiratory disease.	29*
E4	Recovered from feces in sporadic cases of mild paresis.	11
E6	Recovered from feces, occasionally spinal fluid, of patients with mild paresis; from spinal fluid of one patient with severe transient paralysis (Guillain-Barré Syndrome). Caused paresis in monkeys.	1, 13, 14,* 16, 25, 33, 34*
E9	Recovered from feces of patients with mild paresis; from spinal fluid of one patient with moderate residual paresis, one case of cerebellar ataxia and from medulla of infant.	9, 14,* 19, 27, 32, 33, 34*
E11	Recovered from feces of patients with moderate to severe paresis; one fatal bulbo-spinal case confirmed by virus isolation and antibody titer rise.	12, 30
Other types	Many types (e.g., 1, 2, 3, 4, 6, 10) have occasionally produced focal neuronal degeneration in infected monkeys, though often without evident neurological signs.	3,* 35

*Review articles.

†This table was compiled from selected references immediately available to the authors and is not presented as a complete bibliography.

the recovery of Coxsackie A7 virus from 33 patients with aseptic meningitis or suspected poliomyelitis, seven of whom had some degree of paralysis, and one of whom, an infant, died. Coxsackie virus A9 has been recovered from the feces of patients with mild to moderate paralysis for which no other etiologic agent was found.[11,12,18,21] Although other group A Coxsackie viruses have not been directly implicated to date in paralytic illnesses, A2 has been recovered from the CNS of infants who died, and types A4 and A14 as well as A7 have caused extensive neuronal lesions in monkeys.[3,8] Also, the simultaneous recovery of Coxsackie A viruses and poliovirus from poliomyelitis patients in a number of studies has suggested the possibility of a synergism between these agents in the causation of paralysis when infections are concurrent.[3] Experimental support for this hypothesis was provided by Dalldorf and Wiegand,[4] who showed that in monkeys inoculated with an attenuated strain of type 1 poliovirus anterior horn cell lesions developed when Coxsackie A7 or A14 infection was superimposed five days later, whereas none of these virus strains induced paralysis when inoculated singly.

Of the six Coxsackie group B viruses, four types (B2-B5) have been repeatedly recovered from the feces in cases of clinical paralytic poliomyelitis with slight to moderate paresis in which evidence of poliovirus infection was lacking.[11,12,18,21] Steigman[29] recovered B5 virus from a child with persistent residual paresis. Kalter[12] recovered Coxsackie B3 virus from the spinal cord of a five-year-old girl who died after a fulminating clinical course of bulbospinal poliomyelitis. Also several types of group B viruses have been recovered from the brain or the spinal cord as well as from the heart and other tissues of small infants who died of generalized Coxsackie virus infection.[15] In these infections of infants myocarditis usually was dominant in the clinical picture but signs of encephalomyelitis have been noted in about one third of the cases reported, and focal histologic lesions of the brain, brain stem and spinal cord have been found in a high proportion of the cases studied.

With respect to the ECHO viruses, several types (types 4, 6, 9, 11, and 16) have been responsible for outbreaks of aseptic meningitis, and several additional types have been associated with sporadic cases of this syndrome.[14,34] At least eight types, namely, 2, 4, 5, 6, 9, 11, 12 and 18, have been isolated from the spinal fluid during ill-

TABLE 2.—*Virologic Findings in Cases of Clinical Paralytic Poliomyelitis by Vaccination Status. California 1956-1960*

Doses Vaccine (Salk)	Number of Patients	Per Cent of Patients, by Laboratory Result						
		Poliovirus	Nonpoliovirus				Inconclusive	Negative
			Coxsackie	ECHO	Other	Total Nonpolio		
Total	706*	62	4	3	3	10	18	10
None	260	80	2	<1	2	4	10	6
1 dose	122	70	2	2	6	9	15	6
2 doses	177	50	6	7	3	17	21	12
3+ doses	139	37	9	4	2	15	29	19

*Total includes 8 patients whose vaccination status was unknown.

ness.[5,6,14,26] In addition to the usual manifestations of the aseptic meningitis syndrome, mild to moderate paresis of scattered muscle groups has been noted in several types of ECHO virus infections. Disability has usually been minor and transitory, although in some cases mild weakness has persisted for three to six months or longer. Minor degrees of paresis have been linked to ECHO virus types 1,[23] 4,[11] 6,[13,16,33] 9,[9,27,33] and 11.[12] There are several reports, however, of more serious paralytic and encephalomyelitic disease attributed to ECHO viruses. Parker and associates[25] recently reported the recovery of ECHO 6 virus from the feces and spinal fluid of a patient with severe paralysis, clinically classified as the Landry-Guillain-Barre syndrome. Steigman[29,30] has described two fatal cases of apparent bulbospinal poliomyelitis, both in two-year-old children, with flaccid paralysis of the extremities and respiratory insufficiency requiring tracheotomy and placement in a respirator. The spinal cord of one child yielded ECHO 2 virus, and ECHO 11 virus infection was present in the other case. Another fatal illness, seen by Verlinde[32] in Holland, occurred in an eight-month-old infant who died after 24 hours of fever and coma; ECHO 9 was recovered from the medulla. In an extensive epidemic of ECHO 9 infections in Milwaukee in 1957, Sabin and others[27] observed that among 213 patients in hospitals (predominantly with aseptic meningitis) one 20-year-old girl at first was thought to have spinal paralytic poliomyelitis because of spasm of the spinal musculature and weakness of the hips which required the use of crutches for about two months. Five patients had signs suggesting involvement of the cerebellum and vestibular nuclei—such as vertigo, loss of balance, nystagmus and facial grimacing. Cerebellar ataxia was subsequently observed by McAllister[19] in a five-year-old boy whose spinal fluid contained ECHO 9 virus. In experimental infections, ECHO types 6 and 16 produced paresis in macacus monkeys,[1] and focal neuronal lesions not clinically evident have been noted in occasional monkeys infected with various ECHO viruses including types 1, 2, 3, 4, 6, 10, 13.[35]

Frequency of association of nonpolioviruses with paralytic disease

In attempting to assess the frequency of association of various nonpolioviruses with paralytic illness in California on the basis of virologic studies made in our laboratory since 1956, it has been apparent that the results varied appreciably with respect to the patient's age, immunizations against poliomyelitis and the severity of paralysis.

Age. In etiologic studies of clinical paralytic poliomyelitis in California,[18] poliovirus was recovered from about 80 per cent of the patients under five years of age, as compared with 60 to 65 per cent of older children and adults. Brown and associates[2] noted a generally similar age trend in the recovery of poliovirus from patients in the 1958 epidemic of poliomyelitis in Detroit. Coxsackie and ECHO virus infections were also encountered more frequently in paralytic illnesses in children under 15 years of age but there was no pronounced grouping in any age bracket within this age range.[18]

Immunization with poliovirus vaccine (Salk). Poliovirus has been less often recovered and other viral infections more frequently found in cases of paralytic illness in patients immunized against poliomyelitis than in the nonimmunized. This is illustrated in Table 2, which gives the virologic findings in 706 cases of suspected paralytic poliomyelitis studied in this laboratory from 1956-1960. Either by recovery of the virus or demonstration of a significant antibody titer rise, poliovirus infection was confirmed in 80 per cent of the patients in the nonvaccinated group, in about 70 per cent of those who had received one dose of vaccine, in 50 per cent of those who had two doses, and in less than 40 per cent of those who had three or more doses. Conversely, the frequency of nonpoliovirus infections increased from less than five per cent in the nonvaccinated group to 15 per cent in the three-dose group. Although differing in actual percentages, the findings of Brown and associates[2] in the Detroit epidemic in 1958 showed a fairly similar pattern of decrease in the proportion of

TABLE 3.—*Virologic Findings in 802 Cases of Clinical Poliomyelitis According to Type and Severity of Paralysis**

Laboratory Findings	Per Cent Distribution						
		Spinal Paralytic				Bulbar and Bulbo-Spinal	
	Nonparalytic	Minimal	Mild	Moderate	Severe	Mild-Mod.	Severe
Total, per cent	100†	100	100	100	100	100	100
Poliovirus	12	21	36	63	85	86	68
Doubtful evidence of poliovirus	23	29	19	15	8	7	20
Negative	27	17	19	15	5	2	12
Nonpoliovirus	36	26	23	8	0	5	0
Poliovirus and nonpoliovirus	3	7	3	0	1	0	0
Number of cases, total 802	444	70	69	62	73	43	41

*Modified from Magoffin, R. L., Lennette, E. H., Hollister, A. C., and Schmidt, N. J.: An etiologic study of clinical paralytic poliomyelitis, J.A.M.A., 175:269-278, Jan. 28, 1961.

†Percentages are rounded independently and may not add to total.

laboratory-confirmed poliomyelitis cases among immunized patients.

Severity of paralysis. The relatively infrequent implication of nonpolioviruses in cases of severe paralytic disease suggested by the foregoing review of published reports is illustrated by the experience in California, which is summarized in Table 3. These data, from a study of clinical poliomyelitis previously published,[2] show that poliovirus and nonpoliovirus infections were each fairly often (12 per cent to 36 per cent) associated with "nonparalytic poliomyelitis" or with "paralytic cases" in which there was only minor paresis. However, with increasing degrees of paralysis or with bulbar involvement, the frequency of nonpoliovirus infections declined sharply. The higher frequency of nonpoliovirus infections in cases in which there was slight to moderate paresis provides supporting evidence of a causal relationship to this type of illness; if these agents merely represented coincidental infections, a more equal distribution in all categories of severity would be expected.

The proportion of laboratory-confirmed poliomyelitis cases became larger with the increasing severity of paresis and with the appearance of bulbar signs, reaching a maximum of about 85 per cent. Even in the categories of severe spinal paralytic or bulbospinal disease, however, there were some cases, particularly in the vaccinated patients, in which no laboratory evidence of poliovirus or of any other infection was elicited.

Overall incidence of nonpoliovirus infections. Without respect to the variables of age, vaccination status, and severity of paresis, the overall occurrence of nonpolioviruses in 706 cases of paralytic disease studied in this laboratory from 1956 to 1960 is summarized in Table 4. For comparison, the findings in 1,259 cases clinically classified as nonparalytic poliomyelitis or aseptic meningitis are also shown. In the group of paralytic cases, poliovirus infection was confirmed in 62 per cent; in 18 per cent it was neither confirmed nor ruled out

TABLE 4.—*Virologic Findings in Cases of Clinical Paralytic Poliomyelitis and Aseptic Meningitis, California 1956-1960*

Laboratory Results	Paralytic Poliomyelitis		Nonparalytic Poliomyelitis, Aseptic Meningitis	
	Number	Per Cent	Number	Per Cent
Totals	706	100	1,259	100
Poliovirus	437	62	85	7
Other enteroviruses	53	7	488	39
Coxsackie A	2	<1	23	2
Coxsackie B	29	4	342	27
ECHO	22	3	123	10
Mumps	13	2	80	6
Herpes simplex	6	1	8	<1
SLE, WEE	1	<1	7	<1
Dual infections	0	0	16	1
Inconclusive	125	18	305	24
Negative	71	10	270	21

(*i.e.* virus was not recovered and serologic tests were inconclusive); and in 10 per cent results of all tests were negative. In 73 cases (about 10 per cent) evidence of a current infection with some other virus was elicited. These other viruses included a Coxsackie group B virus in 29 cases (4 per cent), a Coxsackie group A virus in three cases (less than one per cent), an ECHO virus in 22 cases (3 per cent), the mumps virus in 13 cases (2 per cent), the virus of herpes simplex in six cases (1 per cent) and the St. Louis encephalitis virus in one case. Altogether, enteroviruses other than poliovirus were found in about 7 per cent, and nonenteric viruses in about 3 per cent of the paralytic illnesses. In cases clinically diagnosed as nonparalytic poliomyelitis or aseptic meningitis, infections with group B Coxsackie viruses, ECHO viruses, or the mumps virus were each found in a much higher proportion of the illnesses, often exceeding poliovirus infections.

The specific immunotypes of viruses encountered each year in paralytic cases are shown in Table 5. In keeping with the pattern commonly found in the United States, type 1 poliovirus infections (360 cases) greatly exceeded type 3 infections (72 cases), and type 2 infections were infrequent (five cases). The other enteroviruses encountered in-

TABLE 5.—*Specific Viruses Associated with Cases of Clinical Paralytic Poliomyelitis. California 1956-1960*

Type of Virus	Number of Patients, by Year					
	Total	1956	1957	1958	1959	1960
Cases studied	706	272	103	102	138	91
Poliovirus	437					
Type 1	360	156	19	44	83	58
Type 2	5	2	1	2	0	0
Type 3	72	22	19	15	12	4
Coxsackie virus	31					
Type A9	1	0	1	0	0	0
Type A16	1	0	0	0	1	0
Type B2	8	2	1	2	2	1
Type B3	2	1	0	1	0	0
Type B4	7	1	5	0	0	1
Type B5	11	4	2	4	0	1
Type B6	1	0	0	0	0	1
ECHO virus	22					
Type 4	7	5	1	0	0	1
Type 6	4	3	0	0	1	0
Type 9	2	0	0	2	0	0
Type 11	1	0	0	0	0	1
Type 13	1	0	0	0	1	0
Type 14	3	1	1	1	0	0
Untyped	4	2	0	0	1	1
Mumps	13	10	2	1	0	0
Herpes simplex	6	0	4	0	1	1
St. Louis enceph.	1	1	0	0	0	0
Total:						
Nonpolioviruses						
No. of patients	73	30	17	11	7	8
Per cent	10%	11%	17%	11%	5%	9%

cluded Coxsackie virus types A9, A16, B2, B3, B4, B5 and B6, ECHO virus types 4, 6, 9, 11, 13 and 14, and several unidentified ECHO types. With the exception of Coxsackie virus types A16 and B6, and ECHO virus types 13 and 14, all of these viruses previously have been associated by various investigators with cases of paralytic illnesses.

COMMENT

The ubiquitous distribution of Coxsackie and ECHO viruses is well known. These agents have frequently been recovered from apparently healthy persons and have been associated with various clinical syndromes in addition to the disorders of the central nervous system discussed herein. Thus it must be emphasized that the demonstration of infection with one of these agents during the course of illness in a patient with a CNS disorder does not constitute proof of a causal relationship. Etiologic significance in each case must be weighed against the possibility of an adventitious infection unrelated to the current illness.

In our opinion, the reports of several well documented instances of recovery of the virus from the brain or spinal cord of man and the demonstration of neurotropic properties in experimentally infected animals (see above) provide convincing evidence that certain types of Coxsackie and ECHO viruses have the capacity to produce neurologic disease which may clinically simulate poliomyelitis. However, factors such as the possibility of coincidental infection and variability in the frequency of infection with respect to age, severity of disease and previous immunization of the patient against poliomyelitis make it extremely difficult to estimate the overall contribution of known types of "nonpolioviruses" to the occurrence of paralytic disease. If etiologic significance were assumed in every instance, in the recent experience of this laboratory, as described above, viruses other than poliovirus might account for about 10 per cent of the illnesses considered clinically to be cases of paralytic poliomyelitis, predominantly cases with slight degrees of paresis. A similar or lesser frequency of nonpoliovirus infections associated with paralytic illness has been observed by other investigators.[2,12,23] Any correction for coincidental infections would, of course, reduce the number of assumed etiologically significant infections. Thus, while there is substantial evidence that viruses other than poliovirus are the causative agents of illnesses clinically simulating paralytic poliomyelitis, nonpolioviruses have not been demonstrated to be major contributors to the overall occurrence of paralytic diseases in recent years.

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